

DETAILED ACTION

This office action is a response to Applicant's amendment submitted April 23, 2008, wherein claims 1 and 12 are amended and new claim 17 is added. Claims 1-17 are pending in this application and are examined on the merits herein.

In view of Applicant's amendment submitted April 23, 2008, the rejection of claim 1 under 35 USC 112, second paragraph, for being indefinite regarding modification of purine or pyrimidine base, is withdrawn.

In view of Applicant's remarks submitted April 23, 2008, the rejection for claims 2, 9, and 16 under 35 USC 112, second paragraph for being indefinite with regard to the limitation $R_1COOC(R_2R_3)-$, is withdrawn. Applicant's argument is persuasive.

In view of Applicant's amendment submitted April 23, 2008, the rejection of claim 1 under 35 USC 112, second paragraph, for being indefinite regarding "optionally substituted," is withdrawn.

In view of Applicant's amendment submitted April 23, 2008, the rejection of claim 12 under 35 USC 112, second paragraph, for lacking antecedent basis is withdrawn.

In view of Applicant's amendment submitted April 23, 2008, the rejection of claim 13 under 35 USC 112, second paragraph, for being indefinite regarding inosine, is withdrawn.

The following rejections of record are maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 10, 11, and dependent claims, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 10, and 11 (and all dependent claims) recite the limitation "optionally substituted." "Optionally substituted" is not defined by the claim or the specification and renders the claim indefinite because it can include substituents which are not actually disclosed and one of ordinary skill in the art would not know what the substituents are. "Optionally substituted" was removed from claim 1 but not from claims 2, 10, and 11 in the amendment submitted April 23, 2008.

Claim Rejections - 35 USC § 103

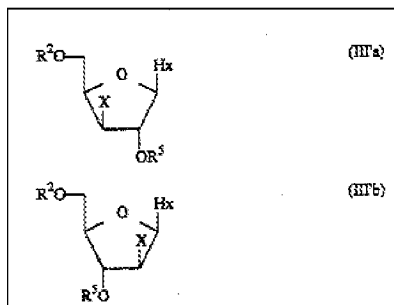
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

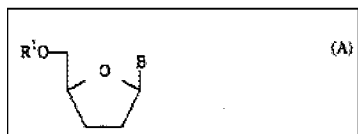
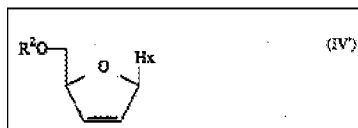
Claims 1-13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honda et al. (US 5,466,793, November 14, 1995, PTO-1449 submitted February 3, 2006) in view of Hrishikesan (US 3,445,186, May 20, 1969, of record).

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Honda et al. teach a process for preparing 2',3'-dideoxyinosines [abstract]. The nucleoside can be unprotected (P=H) or protected with a C₁₋₁₂ acyl group, a C₁₋₁₂ alkyl group, a C₇₋₈ aryl group, or a silyl group [column 4, lines 40-44]. An inosine derivative III'a or III'b, shown below [column 5, lines 45-55], is allowed to react with zinc powder in the presence of acetic acid in an organic solvent. [column 8, line 65 – column 9, line 15] The zinc complex formed in the reaction must be removed because it can interfere with subsequent reactions and forms zinc hydroxide gel when treated with water, which is difficult to remove [column 10, lines 28-38]. The zinc powder is removed by ion-exchange resin, porous nonpolar resin, or chelating agent to give the corresponding 2',3'-didehydro-2',3'-dideoxy-5'-O-acylinosine. The organic solvent used in the reaction can be methanol, ethanol, acetonitrile, THF, DMF, or a mixture thereof. [column 8, line 65 – column 9, line 15] The 2',3'-didehydro-2',3'-dideoxynucleoside inosine derivative IV', shown below [column 5, lines 35-40], obtained by the zinc reaction, is then subjected to reduction with hydrogen over palladium catalyst, followed by hydrolysis or ester exchange reaction to give 2',3'-dideoxyinosine derivative A', shown below [column 5, lines 15-20]. [column 9, lines 16-21]



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In one example, 9-(2',5'-O-diacetyl-3'-bromo-3-deoxy- β -D-xylofuranosyl)hypoxanthine and 9-(3',5'-O-diacetyl-2'-bromo-2'-deoxy- β -D-cylofuranosyl)hypoxanthine was suspended in a mixture of 25 ml acetonitrile and 25 ml methanol, zinc powder, and acetic acid, and stirred for one hour. After workup, 5'-O-acetyl-2',3'-didehydro-2',3'-dideoxyinosine was obtained. This product was suspended in ethanol, $Pd-BaCO_3$ was added, and the mixture was stirred for two hours under a hydrogen gas stream to give 5'-O-acetyl-2',3'-dideoxyinosine. [Column 19 and 20, Examples 3 and 4]. In another example, sodium hydroxide was used to deprotect the product after hydrogenation to give 2',3'-dideoxyinosine [column 20, Example 5]. In another example, the product of the zinc reduction is partially deprotected during the workup, before the hydrogenation reaction [column 20, Example 6].

Honda et al. do not teach removal of zinc using an alkali metal sulfide or an alkaline-earth metal sulfide.

Hrishikesan teach the removal of dissolved zinc from alumina hydrate by adding at least a stoichiometric amount of alkali metal sulfide to cause precipitation of the zinc as zinc sulfide [see abstract]. Sodium sulfide effects the precipitation of zinc as zinc sulfide, which is filtered off [column 2, lines 7-25]. An excess of alkali metal sulfide,

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such as sodium or potassium sulfide, is preferred [column 2, lines 46-54]. Aqueous solution of sodium sulfide was used [column 4, Example 2].

It would have been obvious to one of ordinary skill in the art at the time the invention was made employ sodium sulfide for the removal of zinc in the method taught by Honda et al. Honda et al. teach that excess zinc must be removed from the reaction, and Hrishikesan teaches a method of precipitating zinc as zinc sulfide, which can then be filtered off. The skilled artisan would understand that the zinc removal steps used in the method of Honda et al. and the sodium sulfide zinc removal taught by Hrishikesan could be used interchangeably to arrive at the same result (removal of zinc from the reaction mixture). One of ordinary skill in the art would also understand that removal of the 5' protecting group could be carried out either before or after the hydrogenation reaction and would not be expected to impact the reaction.

Response to Arguments

Applicant's arguments filed April 23, 2008 have been fully considered but they are not persuasive. Applicant argues that modification of the teachings of Hrishikesan would render it unfit for its intended purpose. Modification of Hrishikesan is not the basis for the rejection and thus this argument is not relevant.

Applicant argues that there is no motivation to combine the references. Honda teaches that zinc removal is a necessary and problematic component of the synthesis, and Hrishikesan teaches that zinc can be removed by precipitation with sodium sulfide. Thus, the skilled artisan would have been motivated to remove zinc from the reaction mixture of Honda using sodium sulfide.

Applicant argues that Honda and Hrishikesan are drawn to different fields of endeavor and problems solved. Both Honda and Hrishikesan are drawn to process which require removal of zinc. Hrishikesan provides a different solution for removal of zinc, which could be employed by the skilled artisan in the method of Honda.

Applicant's arguments regarding temperature are moot because the rejected claims do not contain a temperature limitation.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Honda et al. (US 5,466,793, November 14, 1995, PTO-1449 submitted February 3, 2006) in view of Hrishikesan (US 3,445,186, May 20, 1969, of record) as applied to claims 1-13, 15 and 16 above, and further in view of Bertolini et al. (WO 01/77103 A1, October 18, 2001, of record).

Honda et al. and Hrishikesan teach as set forth above.

Honda et al. do not teach the use of ammonium salt or phosphonium salt as activating agents in the zinc reaction.

Bertolini et al. teach a process wherein 2'-deoxy-2'-bromo-3',5'-diacetyl-5-methyluridine is converted into 5'-acetylstavudine by reductive elimination in the presence of zinc as reducing agent combined with an ammonium salt or phosphonium salt as the activating agent [page 2, lines 5-11].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use ammonium salt or phosphonium salt as the activating agent, instead of acetic acid, in the method of Honda et al. Both Honda et al. and Bertolini et

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al. teach reductive elimination using zinc in the presence of an activating agent, but each of the references teaches a different activating agent. The skilled artisan would understand that the reactions taught by Honda et al. and Bertolini et al. are analogous reactions and that the activating agents could be used interchangeably and successfully in the zinc reaction.

Response to Arguments

Applicant's arguments are the same as addressed above.

The following is a new rejection necessitated by the addition of new claim 17 in Applicant's amendment submitted April 23, 2008.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-13 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honda et al. (US 5,466,793, November 14, 1995, PTO-1449 submitted February 3, 2006) in view of Veeken et al. (Water Research 37 (2003) 3709-3717).

Honda et al. teach as set forth above.

Honda et al. do not teach removal of zinc using an alkali metal sulfide or an alkaline-earth metal sulfide.

Veeken et al. teach sulfide precipitation for removal of zinc in wastewaters [see abstract and page 3709, second paragraph]. Sulfide sources such as Na_2S , NaHS , CaS , FeS , or H_2S can be employed [page 3710, first paragraph]. Sulfide precipitation was studied at room temperature [page 3710, last paragraph].

It would have been obvious to one of ordinary skill in the art at the time the invention was made employ sodium sulfide for the removal of zinc in the method taught by Honda et al. Honda et al. teach that excess zinc must be removed from the reaction, and Veeken et al. teaches a method of precipitating zinc as zinc sulfide, which can then be filtered off. The skilled artisan would understand that the zinc removal steps used in the method of Honda et al. and the sodium sulfide precipitation taught by Veeken et al. could be used interchangeably to predictably arrive at the same result (removal of zinc from the reaction mixture). Zinc sulfide is known in the art to be insoluble in both water and ethanol, and Honda et al. teach a limited number of preferred solvents, such as acetonitrile and ethyl acetate. One of ordinary skill in the art would also understand that removal of the 5' protecting group could be carried out either before or after the hydrogenation reaction and would not be expected to impact the reaction. Although Veeken et al. teach zinc precipitation at 25°C and are silent regarding the use of higher temperatures, $40\text{--}60^\circ\text{C}$ is a fairly mild temperature increase over the teachings of Veeken et al. and could easily be arrived at via routine experimentation. See MPEP 2144.05: Generally, differences in concentration or temperature will not support the

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patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Honda et al. (US 5,466,793, November 14, 1995, PTO-1449 submitted February 3, 2006) in view of Veeken et al. (Water Research 37 (2003) 3709-3717) as applied to claims 1-13, 15 and 16 above, and further in view of Bertolini et al. (WO 01/77103 A1, October 18, 2001, of record).

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each of the references teaches a different activating agent. The skilled artisan would understand that the reactions taught by Honda et al. and Bertolini et al. are analogous reactions and that the activating agents could be used interchangeably and successfully in the zinc reaction.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on T-F 9:00-5:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623

/Layla Bland/
Examiner, Art Unit 1623